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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,451	01/27/2004	Craig A. Townsend	62732.000152	8691

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

MAIL DATE	DELIVERY MODE
05/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,451	TOWNSEND ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-31,33-36,38-40,42,43 and 46-48* is/are pending in the application.

4a) Of the above claim(s) *25-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30, 31, 33-36, 38-40, 42, 43, 46-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

JON EPPERSON
PRIMARY EXAMINER

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *23 February 2007*.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed February 26, 2007 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 25-31 and 33-48 were pending. Applicants amended claim 30, 31, 39, 40, and 43. In addition, In addition, Applicants canceled claims 37, 41, 44, and 45. No claims were added. Therefore, claim 25-31 and 33-36, 38-40, 42, 43, 46-48 are currently pending. Furthermore, claims 25-29 remain withdraw from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species and/or inventions, there being no allowable generic claim. Therefore, claims 30, 31, 33-36, 38-40, 42, 43, 46-48 are examined on the merits.

4. Please note that this application contains claims 25-29 drawn to a nonelected invention(s). This was addressed in the previous action (see 11/3/04 Restriction). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01. Please note that rejoinder is only available for method claims, not products (i.e., claims 25-29) in accordance MPEP § 821.04(b).

Withdrawn Objections/Rejections

5. The rejection denoted "A" under 35 U.S.C. § 112, second paragraph is withdrawn in view of Applicants' amendments to or cancellation of claims 40, 44, and 45. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112, first paragraph

6. Claims 30, 31, 33-36, 38-40, 42, 43, 46-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds that inhibit a narrow range of mycobacterium including *tuberculosis*, *bovis* and *avium-intracellulare* "*in vitro*", does not reasonably provide enablement for the treatment of "any" mycobacterial infection using the full scope of the claimed compounds "*in vivo*" (i.e., a method of treatment). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". Some of these factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention

based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) The breadth of the claims and the nature of the invention: The claims are broad because they include the treatment of "any" pathogentic mycobacterial-based infection caused by *M. tuberculosis*, drug resistant *M. tuberculosis*, *M. bovis*, *M. Leprae*, and *M. paratuberculosis* in "any" animal, which would encompass a large number of unrelated etiologies. Consequently, the nature of the invention cannot be fully determined because the invention has not been defined with particularity.

(3 and 5) The state of the prior art and the level of predictability in the art: The prior art indicates that Applicants' claimed compounds can only be used to inhibit a very narrow range of mycobacterial species "in vitro" including *tuberculosis*, *bovis* and *avium-intracellulare* (e.g., see Jones, P. B.; Parrish, N. M.; Houston, T. A.; Stapon, A.; Bansal, N. P.; Dick J. D.; Townsend, C. A. "A New Class of Antituberculosis Agents" *J. Med. Chem.* **2000**, *43*, 3304-3314, page 3308, column 1, last full paragraph, "The compounds marked with an asterisk in Table 1 [i.e., Applicants' claimed compounds] were also tested against other bacterial strains including *Staphylococcus aureus* (ATC 29213), *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853). None exhibited any activity against these bacteria"; see also page 3309, column 1, paragraph 1, "... these compounds are highly species-specific [i.e., Applicants' claimed compounds], showing no activity against other bacteria including strains of nonpathogentic mycobacteria, such as *M. smegmatis* [i.e., no activity even for other closely related mycobacteria]"; see also Table 1 in specification).

Furthermore, Rieder states that no correlation exists between *in vitro* and *in vivo* test results for anti-tuberculosis (e.g., see Rieder H. L. (**2002**) Interventions for tuberculosis control and elimination, International Union Against Tuberculosis and Lung Disease, Paris, pages 45 and 46, especially page 46, paragraph 1, "The correlation between *in vitro* and *in vivo* results is often very poor"). This is further supported by Nuermberger et al. (Nuremberger et al. "Pharmacokinetic andPharmacodynamic Issuesin the Treatment of Mycobacterial Infections" *Eur. J. Clin. Microbiol. Infect. Dis.* **2004**, *23*, 243-255) stating, "there are no convincing *in vitro* models to predict the sterilizing activity of antituberculous drugs. Murine models are able to predict sterilizing activity, but the necessary experiments are lengthy, labor intensive, and expensive" (e.g., see Nuermberger et al., page 247, column 1, paragraph 1). The problem, according to Nuermberger, stems from the fact that unlike fast growing bacteria, Mycobacterium tuberculosis "has a prolonged doubling time, the potential for intracellular replication, and the capacity for dormancy" (e.g., see Nuermberger et al., page 246, column 2, last paragraph), which makes these microbes especially difficult to treat. Consequently, Nuermberger et al. conclude, "more work is needed to determine if the degree to which drugs concentrate intracellularly and kill intracellular bacilli *in vitro* correlates with bactericidal or sterilizing activity in animal models or clinical studies"). Burman (Burman, W. J. "The value of in vitro drug activity and pharmacokinetics in predicting the effectiveness of antimycobacterial therapy: a critical review" *Am. J. Med. Sci.* **1997**, *313(6)*, 355-363) also supports these ideas stating, "Conventional in vitro assays of antituberculous activity measure the activity of a drug against extracellular, rapidly

dividing bacilli. A reasonable correlation exists between activity under these conditions and "early bactericidal activity" in vivo ... [However,] [t]he value of early bactericidal activity as an indicator of the efficacy of a drug or drug combination remains speculative" (e.g., Burman, page 357, column 1, last two paragraphs). Burman further states, "The primary limitation of standard in vitro assays and early bactericidal activity is that neither predicts sterilizing activity" (e.g., see Burman, page 357, column 2, paragraph 2). Burman also notes "the use of intracellular assays does not substantially improve the predictive values of in vitro assessments of drug activity" (e.g., see Burman, page 358, column 1, last paragraph). For example, Burman notes that Isoniazid is a remarkably potent compound in vitro but has little sterilizing activity in vivo (e.g., see Burman, page 358, column 2, last paragraphs). Thus, Burman concludes "New tests of antimycobacterial drug activity that assess sterilizing activity are needed urgently to identify new drugs and formulate new treatment regiments" (e.g., see Burman, page 360, column 1, last paragraph).

Furthermore, even if, *assuming arguendo*, a correlation could be established between "in vitro" and "in vivo" results for tuberculosis (which is not the case, see above), this does not mean that such a correlation exists for the other species. For example, Nuermberger et al. state, "individual species have unique patterns of antimicrobial susceptibility, which necessitates specialized treatment regimens even among the mycobacterial genus. For many species, the optimal treatment regimens have yet to be defined." (e.g., see Nuermberger et al., page 243, column 2, paragraph 2). Nuermberger et al. further state, "The therapy of mycobacterial infections is challenging

... procedures for drug susceptibility testing and optimal treatment regimens have yet to be defined ... because mycobacteria are generally slow to succumb to antimicrobial agents, therapy must be given with multiple drugs for prolonged period of time, making it necessary to monitor for drug toxicity, drug interactions, and patient nonadherence" (e.g., see abstract).

Finally, the prior art indicates that the mechanisms by which drugs act to inhibit a mycobacterial infection are also poorly understood (e.g., see Fernanda et al., "Construction of a promoter trap to identify virulence genes in mycobacterium tuberculosis", Molecular Mechanisms in Tuberculosis Keystone Symposium, February 19-25, 1995, Tamarron Colorado, "Despite intense biological and biochemical research, the pathogenesis of mycobacterial disease remains poorly understood"). Even as late as 2001, experts in the field acknowledge that the art is still in its infancy and that the mechanism of action of closely related compounds is unknown (e.g., see Parrish et al. "In vitro Activity of a Novel Antimycobacterial Compound, N-Octanesulfonylacetamide, and Its Effects on Lipid and Mycolic Acid Synthesis" Antimicrobial Agents and Chemotherapy **2001**, 45(4), 1143-1150, especially paragraph bridging columns 1 and 2 on page 1149, "OSA-mediated inhibition of mycolate synthesis in BCG and MAC may involve an as-yet unidentified enzyme or enzyme system [i.e., mechanism of action is unknown]. In summary, the effects of OSA, cerulenin, and thiolactomycin are mycobacterial species specific and compound specific and inherent differences in the mycolic acid biosynthetic pathway may exist between rapid and slow-growing mycobacteria").

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants provide only a narrow ranges of examples where their claimed compounds are used "in vitro" to inhibit *tuberculosis*, *bovis* and *avium-intracellulare* (e.g., see specification, Table 1 wherein only MTB, BCG and MAI are disclosed). No "in vivo" data is presented.

(8) The quantity of experimentation needed to make or use the invention base on the content of the disclosure: As a result of the broad and unpredictable nature of the invention and the lack of specific guidance from the specification, the Examiner contends that the quantity of experimentation needed to make and or use the invention would be great. Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991). Where physiological activity is concerned (i.e., the claimed method of treatment), one skilled in the art reasonably would not and properly should not accept *in vitro* results as support for *in vivo* activity. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, Ltd., 927 F.2d 1200, 1216-1217, 18 USPQ2d 1016, 1030 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Therefore, to enable one skilled in the art to use a method of treating pathogenic mycobacterial infections *in vivo* based solely on *in vitro* testing, as is the case here, some evidence correlating *in vivo* results to *in vitro* testing at the pertinent time is required. See *In re Brana*, 51 F.3d 1560, 1565 USPQ2d 1437, 1442

(Fed. Cir. 1995)(to enable one skilled in the art to use a clinical method based on preclinical testing, the preclinical testing must be shown to be statistically significant) and *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051, 224 USPQ 739, 747-748 (Fed. Cir. 1985) (preclinical testing activity must at least reasonably correlate to clinical activity to establish utility). Here, as noted above, Applicants have failed to provide any "correlation" between inhibiting a narrow range of slow-growing mycobacteria "*in vitro*" to treating the currently claimed broad range of organisms "*in vivo*." Furthermore, the prior art indicates that no such correlation exists (see sections 3 and 5 above and references contained therein).

Response

7. Applicant's arguments directed to the above Enablement rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue, "Applicants have canceled claims 44 and 45" (e.g., see 2/26/07 Response, paragraph bridging pages 7 and 8).

[2] Applicants argue, "Applicants have amended claims 30 and 31 to change the definitions of "R," "Z," and "Y" groups ... as amended, the claims do not cover compounds 12, 28, 29, or 30 in the Parish references" (e.g., see 2/26/07 Response, page 8, paragraph 2).

[3] Applicants argue, "the claims as amended do not include M. avium-interacellulare, and respectfully submit that the rejection on this basis should be withdrawn" (e.g., see 2/26/07 Response, page 8, last paragraph).

[1-3] The Examiner has amended the above rejection to reflect these changes.

[4] Applicants argue, "Kurashima states that in vitro sensitivity does correlate with in vivo sensitivity for Mycobacterium tuberculosis" (e.g., see 2/26/07 Response, page 8, last paragraph)

[4] The Examiner respectfully disagrees. Kurashima look at select compounds interacting with select species. It does not view the landscape as a whole. Prior art references like the Burman review article (see newly amended rejection above) clearly indicate that in vitro tests provide a poor indication of in vivo activity. Where physiological activity is concerned (i.e., the claimed method of treatment), one skilled in the art reasonably would not and properly should not accept *in vitro* results as support for *in vivo* activity. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, Ltd., 927 F.2d 1200, 1216-1217, 18 USPQ2d 1016, 1030 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). Therefore, to enable one skilled in the art to use a method of treating pathogenic mycobacterial infections *in vivo* based solely on *in vitro* testing, as is the case here, some evidence correlating *in vivo* results to *in vitro* testing at the pertinent time is required. See *In re Brana*, 51 F.3d 1560, 1565 USPQ2d 1437, 1442 (Fed. Cir. 1995)(to enable one skilled in the art to use a clinical method based on preclinical testing, the preclinical testing must be shown to be statistically significant) and *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051, 224 USPQ 739, 747-748 (Fed. Cir. 1985) (preclinical testing activity must at least reasonably correlate to

clinical activity to establish utility). Here, as noted above, Applicants have failed to provide any "correlation" between inhibiting a narrow range of slow-growing mycobacteria "*in vitro*" to treating the currently claimed broad range of organisms "*in vivo*." Furthermore, the prior art indicates that no such correlation exists (see sections 3 and 5 in the newly amended rejection above).

Accordingly, the Enablement rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
May 18, 2007

JON EPPERSON
PRIMARY EXAMINER